Ethylene Oxide
Carcinogenic Dose-Response Assessment

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Acronyms and Abbreviations

Acronyms and Abbreviations	Definitions
AMCV	air monitoring comparison value
°C	degrees Celsius
CES	critical effect size
DNA	deoxyribonucleic acid
DSD	development support document
ESL	effects screening level
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based effects screening level for nonthreshold dose response cancer effect
EtO	ethylene oxide
HEV	hemoglobin N-(2-hydroxyethyl)-valine
IARC	International Agency for Research on Cancer
LCL	lower confidence limit
LHN	lymphohematopoietic neoplasms
MW	molecular weight
µg	microgram
µg/m^3	micrograms per cubic meter
mg	milligrams
mg/m^3	milligrams per cubic meter
MLE	maximum likelihood estimate
mm Hg	millimeters of mercury
MOA	mode of action
n	number
N/A	Not applicable
NATA	National Air Toxics Assessment
NIOSH	National Institute for Occupational Safety and Health
NHL	non-Hodgkin's lymphoma

OSHA	Occupational Safety and Health Administration
PEL	permissible exposure level
POD	point of departure
ppb	parts per billion
ppm	parts per million
RR	risk ratio
SAB	Science Advisory Board
SAS	Statistical Analysis System
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SIR	standardized incidence ratio
SMR	standardized mortality ratio
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UCC	Union Carbide Corporation
URF	unit risk factor
USEPA	United States Environmental Protection Agency
USFDA	US Food & Drug Administration
WHO	World Health Organization
WV	West Virginia

Chapter 1 Key Findings, Executive Summary, and Summary Tables

Executive Summary

- Ethylene oxide (EtO) is a chemical with many industrial applications and is particularly useful as a sterilant for medical devices.
- Because EtO is emitted in Texas and has been determined to be a carcinogen, the TCEQ undertook a carcinogenic dose-response assessment and derivation of a unit risk factor (URF) and an effect screening level (ESL) for this chemical.
- Review of the EtO literature demonstrated that EtO operates by a direct-acting mutagenic mode of action (MOA) and suggests that the EtO cancer dose-response should be no more than linear overall with sublinearity expected by both the TCEQ and USEPA (2016) at endogenous levels and below.
- In addition, EtO is produced endogenously, and an ambient air concentration of ≈1.3 ppb would be required to increase the internal dose of EtO by 1 standard deviation. Therefore, ambient EtO concentrations significantly less than 1 ppb (e.g., USEPA's acceptable air concentrations of 0.0001-0.01 ppb) would not be expected to produce biologically meaningful internal doses considering the range of normal endogenously-produced background EtO levels.
- Consistent with TCEQ guidelines (TCEQ 2015), recently derived toxicity factors and guideline air levels were reviewed to determine if there is a toxicity factor or guideline air level that is suitable for adoption by the TCEQ. As such, the USEPA's recently completed Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (USEPA 2016) was reviewed. The USEPA derived a URF of 9.1E-3 per ppb (lymphoid and breast cancer, ADAF adjusted), which corresponds to a 1 in 100,000 excess cancer risk air concentration of 0.001 ppb.
- The human data available for deriving an EtO toxicity factor are from two very high exposure occupational cohorts (Union Carbide Corporation (UCC) and National Institute for Occupational Safety and Health (NIOSH)) that provide no information about the shape of the dose-response curve at low (i.e., environmentally-relevant) EtO concentrations. The TCEQ agrees with USEPA's determination that in the low-dose range a sublinear dose-response is "highly plausible," based on the MOA and information about endogenous production of EtO.
- In contrast to their determination that the low-dose region of the EtO dose-response curve is highly plausibly sublinear, USEPA ultimately chose to model EtO-induced lymphoid cancer with an overall supra-linear two-piece spline model that has a very steep linear slope in the low-dose region.

- The TCEQ evaluated USEPA's URF and overall supra-linear (i.e., linear two-piece spline) modeling choice in the context of the available observed data to determine the validity of the modeling and URF:
    - Endogenous Levels of EtO – USEPA's URF estimates that ambient concentrations of EtO > 0.01 ppb would produce an unacceptable increased cancer risk of greater than 1 in 10,000. This estimated ambient EtO concentration corresponds to an internal dose that is over 30 times lower than the 1st percentile of normal endogenous background levels (non-smokers), which is highly unlikely to be biologically meaningful and is inconsistent with the assessment of excess risk.
    - Population-Level Lymphoid Cancer Risk – Using measured concentrations of a biomarker of internal EtO exposure (an EtO-specific protein adduct in blood), it can be estimated that the mean amounts of background EtO levels would be equivalent to ambient concentrations of EtO of 1.9 ppb in non-smokers and 18.8 ppb in smokers. Accordingly, at measured background levels of EtO, the USEPA's URF for lymphoid cancer (7.1E-03 per ppb, ADAF adjusted) would predict a population-wide lymphoid cancer incidence rate of ≈3.8% (in the absence of any exogenous EtO ambient air exposure or other potential causes of lymphoid cancer). By contrast, the USEPA-cited lymphoid cancer background incidence rate (which would have many contributing factors, not just a single chemical) is 3%, demonstrating that USEPA's URF overestimates observable lymphoid cancer risk based on endogenous/background levels of EtO alone.
    - Lymphoid Cancer Risk from Cohort Studies – The UCC cohort shows no statistically significant increased risk of lymphoid cancer with EtO exposure. The NIOSH cohort shows statistically significant increased risk of lymphoid cancer mortality at relatively high cumulative exposures. These data are not consistent with USEPA's selected model assessment (i.e., upper bound on the linear two-piece spline model) because that model assessment would predict statistically increased risks at even the lowest EtO cumulative exposures (see below).
    - Model Fit with Observed Data – USEPA conducted their EtO cancer dose-response modeling using the NIOSH cohort data. To verify that USEPA's final selected model assessment (i.e., upper bound on the linear two-piece spline model) properly fit the original data, it was used to predict the expected number of lymphoid cancer deaths based on the same NIOSH individual exposure data as USEPA used for modeling. *Whereas 53 lymphoid cancer deaths were observed* in this cohort of 17,530 workers, *USEPA's selected dose-response model assessment predicted 141* (95% confidence interval (CI) of 108, 188) lymphoid cancer deaths in this same cohort. Similarly, USEPA's final selected model assessment statistically significantly over-predicts lymphoid cancer deaths in every cumulative exposure quintile and indicates that statistically increased lymphoid cancer mortality should have occurred in every exposure quintile (including the

lowest), when in fact this did not occur. This demonstrates unequivocally that USEPA's selected model assessment cannot be validated by the data that was used to derive it, and this model is not appropriate to use for estimates of population risk.

- The TCEQ determined that USEPA's use of an overall supra-linear dose-response model (i.e., the upper bound of the linear two-piece spline model) to derive their URF: 1) is not justified by the MOA data (which support a no-more-than linear dose-response); 2) is not consistent with predicted population risk from endogenous EtO for lymphoid cancer; and 3) statistically significantly over-estimates the number of lymphoid cancer deaths in the cohort from which the dose-response model was derived. **Therefore, the TCEQ found that USEPA's EtO inhalation URF is not adequately supported by scientific data and the TCEQ did not adopt it for this evaluation.**
- The TCEQ conducted a systematic review for studies that could inform the derivation of a cancer URF for inhalation exposures to EtO. This review identified key epidemiological data from two cohorts of occupationally-exposed workers, and Cox proportional hazards modeling was conducted to model the EtO-cancer dose-response.
- The TCEQ ultimately chose lymphoid cancer mortality as the critical cancer endpoint, using a 15-year EtO exposure lag with results for NIOSH males being more conservative, to calculate a **URF of 2.5E-6 per ppb (1.4E-6 per ug/m^3)** and a **$^{chronic}ESL_{nonthreshold(c)}$ of 4 ppb (7 ug/m^3)** at an excess cancer risk level of 1 in 100,000.
- As with USEPA's URF, the TCEQ's URF was evaluated in the context of the available observed data to determine the validity of the modeling and URF:
  - Endogenous Levels of EtO – Compared to endogenous EtO levels, the TCEQ's ESL of 4 ppb would produce an internal exposure equivalent to between the 90th-95th percentile of the normal endogenous range and could biologically plausibly be associated with excess risk above and distinguishable from normal endogenous EtO contributions to background risk.
  - Population-Level Lymphoid Cancer Risk - At measured endogenous levels of EtO, the TCEQ's URF would predict a population-wide lymphoid cancer rate that is lower than the background population lymphoid cancer rate (unlike USEPA's URF).
  - Lymphoid Cancer Risk from Cohort Studies – The standard Cox proportional hazards model of lymphoid cancer mortality did not show a relationship with EtO exposure that was statistically significantly different from zero. Therefore, by assuming a significant positive slope in the EtO-cancer association, the TCEQ is making a conservative decision to assume that EtO is causing lymphoid cancer in the exposed workers in the NIOSH cohort. Adding to this conservatism is the TCEQ's decision to use an upper confidence limit on the slope.

- Model Fit with Observed Data – To verify that the TCEQ's model properly fit the original data, the expected number of lymphoid cancer deaths based on the individual exposure estimates for the NIOSH cohort (also used by USEPA) were calculated. Whereas *53 lymphoid cancer deaths were observed* in this cohort of 17,530 workers, *the TCEQ's selected dose-response assessment (i.e., upper bound of the Cox proportional hazard model) predicted 59* (95% CI of 45, 78) lymphoid cancer deaths. Similarly, TCEQ's selected assessment neither significantly over- or under-estimated lymphoid cancer deaths for any exposure quintile. This demonstrates that the TCEQ's model selection provides a superior fit to the observed number of lymphoid cancer deaths in the NIOSH cohort.

- The TCEQ determined that the use of Cox proportional hazards models to derive a URF for inhalation EtO cancer risk: 1) is justified by the MOA data showing EtO to be a direct-acting carcinogen whose effects, particularly at doses near the endogenous range, would be buffered by cellular repair mechanisms; 2) is consistent with population background risk considering background endogenous EtO levels (i.e., does not overestimate population risk for lymphoid cancer mortality); and 3) accurately estimates the number of lymphoid cancer deaths in the cohort from which the dose-response model was derived. **Therefore, the TCEQ's EtO URF has a sound scientific basis and will be adopted for review of air concentration data and for use in air permit reviews.**

Summary of Key Points

In 2016, the USEPA derived an inhalation URF for EtO (9.1E-03 per ppb or 5.0E-03 per µg/m^3; p. 4-91 of USEPA 2016) based on an overall supra-linear two-piece spline model (USEPA 2016). The URF is primarily driven by USEPA's dose-response assessment of lymphoid cancer in the NIOSH cohort. Despite extensive review by the USEPA Science Advisory Board (SAB) and extensive public comments on the science, in this Development Support Document (DSD) the TCEQ is able to demonstrate that *the model assessment ultimately selected by USEPA* (i.e., the upper bound of the linear two-piece spline model with the "knot" at 1,600 ppm × days, 15-year exposure lag) *statistically significantly over-estimates the actual number of lymphoid cancer mortalities observed in the NIOSH cohort; predicting 141 (95% CI of 108, 188) if USEPA's model were accurate versus the 53 actually observed (Figure 8). By contrast, the model assessment selected by the TCEQ* (i.e., the upper bound of the Cox proportional hazards model, 15-year exposure lag) based on relevant considerations discussed herein *predicts 59 lymphoid cancer mortalities versus the 53 actually observed*. Furthermore, *the USEPA's model assessment statistically significantly over-predicts lymphoid cancer mortality in every NIOSH cumulative exposure group, whereas the TCEQ's model assessment neither statistically over- or under-predicts for any cumulative exposure group (Figures 9-12).*

Supra-linear models are generally not biologically plausible and tend to grossly overestimate low-dose risks. Therefore, sufficient mechanistic or biological data are required to support the application of a supra-linear model (i.e., the steep lower-dose component) for low-dose extrapolation (TCEQ 2015). USEPA (2016) provides no solid mechanistic or biological foundation for adopting an overall supra-linear dose-response model, particularly its steep slope in the range of interest (e.g., typical environmental levels). In fact, *USEPA acknowledges the lack of mechanistic data to support the biological plausibility of a supra-linear dose-response,* stating *"the EPA is not aware of a mechanistic explanation"* and citing *"insufficient information to elucidate a basis"* (pp. I-29 and I-34 of USEPA 2016). Indeed, all the relevant considerations (e.g., MOA, normal endogenous background levels) discussed in various sections of this DSD consistently support the conclusion that there is a lack of data to adequately support the application of a supra-linear model with its steep low-dose slope to extrapolate to significantly lower (e.g., ambient air) EtO doses. Moreover, the available dose-response data from the NIOSH cohort (e.g., Steenland et al. 2004) are not informative as to the shape of the dose-response curve across doses of true interest (e.g., in the range of typical environmental concentrations), which USEPA acknowledged (p. I-14 of USEPA 2016; see Section 3.4.1.4.1). Workers were exposed to extraordinarily high concentrations of EtO, with exposure means ≈1,000,000-2,000,000 times higher than central tendency environmental exposures (animal carcinogenicity data are at even higher mean concentrations) and daily job exposures ranging from ≈15,000-32,000,000 times higher than central tendency environmental exposures. High-dose carcinogenicity data alone are incapable of informing truly low-dose risk, no matter how extensive the analyses or peer review (i.e., other relevant information such as mechanism/MOA must be duly considered). Indeed, USEPA acknowledges that *"the actual exposure-response relationship at low exposure levels is unknown"* (pp. 4-61 and 4-74 of USEPA 2016). *USEPA (2016) should not have based a URF on a supra-linear model (i.e., its lower-dose component) without a robust mechanistic justification for expecting its steep low-dose slope at truly low doses nor should the USEPA have used it to make a large low-dose extrapolation across an area (i.e., the endogenous range) where the agency in fact considers sublinearity "highly plausible."*

However, USEPA did ultimately derive a URF based on a supra-linear model (i.e., the lower-dose slope of the linear two-piece spline model), which necessarily leads to the following implausible conclusions when considering endogenous levels of EtO:

- *The air concentration at the maximum acceptable excess risk (0.01 ppb at 1E-04 risk) corresponds to an internal dose that is over 30 times lower than even the 1st percentile of normal endogenous background levels* (see Section 3.4.1.2.2);
- Expressed in other terms, based on USEPA (2016) and data on normal endogenous background levels, *air concentrations corresponding to more than ≈0.5% percent of mean normal endogenous background levels in nonsmokers would be considered to be associated with unacceptable risk*; and

- *The predicted lymphoid cancer incidence based on mean background levels alone is greater than the population background rate cited by USEPA* (see Section 3.4.1.2.1).

The statistically significant overestimation of risk, *driven by a lymphoid cancer model for which there is inadequate statistical evidence that the slope is even greater than zero in the NIOSH (or UCC) cohort* (Appendix 5), undermines accurate risk communication and can lead to unintended societal consequences.

Consistent with the discussion above, the TCEQ has derived an inhalation URF for EtO because currently available information indicates that the existing USEPA URF results in biologically implausible risk estimates at environmentally-relevant air concentrations where use of the steep low-dose slope from an overall supra-linear two-piece spline model is not justified. For example:

- *The air concentrations corresponding to the USEPA acceptable excess risk range* (1 in a million to 1 in 10,000 based on the USEPA 2016 URF) *are orders of magnitude below those corresponding to the normal endogenous background range* (see Figure 7), making minuscule contributions to internal exposure that are not biologically meaningful as resulting total exposures are indistinguishable from normal endogenous background;
- Statistically significant increases in critical cancer endpoints observed in the NIOSH cohort occur at carcinogenic cumulative exposures that are *orders of magnitude above* endogenous levels (below which USEPA extrapolates orders of magnitude), and USEPA had no truly low-dose data to inform the shape/slope of the dose-response over the normal endogenous background range much less near typical environmental or risk-based air concentrations, which are even lower;
- The *biological implausibility of an overall supra-linear model for extrapolating risk down to endogenous levels* (and lower environmental and risk-based levels) is in fact supported by USEPA stating, "EPA considers it *highly plausible* that the dose-response relationship over the endogenous range is *sublinear*"; contrary to USEPA's expectation, the USEPA (2016) URF is based on a supra-linear model (i.e., the steep lower-dose linear component) that was used to extrapolate over the endogenous range and even below; and
- Consequently, *when USEPA's URF is used in conjunction with population-weighted mean background levels in nonsmokers and smokers, a background lymphoid cancer incidence greater than the USEPA-cited background incidence is predicted based on background levels alone* (see Section 3.4.1.2.1), which suggests a *scientifically unreasonable* URF.

Moreover, USEPA may not have adequately explored the potential contributions of ethylene to EtO risk, stating "only ≈3% of exogenous ethylene was converted to EtO in workers exposed to

0.3 ppm" and that "exogenous ethylene exposure is unlikely to contribute significantly to the effects associated with exposure to exogenous EtO in humans" (p. 3-30 of USEPA 2016). *However, based on USEPA's URF, mean environmental concentrations of ethylene in many areas would in fact result in unacceptable excess risk estimates when multiplied by 0.03 to account for the USEPA-cited endogenous conversion of 3% of exogenous ethylene to EtO.* More specifically, greater than a 1E-04 excess risk would be estimated by USEPA's EtO URF at long-term ethylene air concentrations greater than 0.37 ppb. Interestingly, mean ethylene concentrations reported in human breath (e.g., 23 ppb in Fenske and Paulson 1999, baseline mean of 29-32 ppb reported in Bratu 2019) exceed this 1E-04 excess risk concentration by over 60-fold. These and other considerations are discussed in more detail within this DSD. *The TCEQ concludes that available information (e.g., mechanistic, biological) does not adequately support use of a supra-linear model (i.e., the steep lower-dose slope of the linear two-piece spline model) for extrapolation to truly low (e.g., environmental) air concentrations.* Consequently, the TCEQ conducted a systematic review of the EtO human cancer literature and derived an appropriate URF based on mechanistic and biological information using models that were consistent with the available data.

The TCEQ URF for EtO based on lymphoid cancer is 2.5E-06 per ppb (1.4E-06 per µg/m^3) and results in a risk-based air concentration of 4 ppb at the no significant excess risk level of 1 in 100,000 (TCEQ 2015). The internal dose from continuous exposure to this EtO air concentration would correspond to the upper end of the endogenous range (i.e., between the 90th and 95th percentile), which is more biologically plausibly consistent with the assessment of excess (i.e., above and distinguishable from EtO background) risk. *The TCEQ-selected dose-response assessment (i.e., upper bound of the Cox proportional hazards model, 15-year exposure lag) accurately predicts the underlying cohort dose-response data (Figures 8-12).*

Table 1 provides a summary of the risk-based value from a chronic, carcinogenic evaluation of EtO for use in air permitting and air monitoring. Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015) for an explanation of the various values used for review of ambient air monitoring data and air permitting. Table 2 provides summary information and the physical/chemical data of EtO.

Table 1: Chronic Health-Based Screening Values for EtO

Screening Level Type	Duration	Value 1 (µg/m^3)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
$^{chronic}ESL_{nonthreshold(c)}$ [a]	**70 yr**	**7**	**4**	**P,M,R**	**A,S,D**	**--**	**Lymphoid cancer in occupationally-exposed workers**	**--**

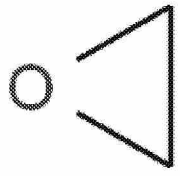
Bold values used for air permit reviews; values have been rounded to one significant digit.

[a] Based on the URF of 1.4E-06 (µg/m^3)$^{-1}$ or 2.5E-06 (ppb)$^{-1}$ and a no significant risk level of 1 in 100,000 excess cancer risk.

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 2: Chemical and Physical Properties

Parameter	Value	Reference
Molecular Formula	C_2H_4O	ATSDR 1990
Chemical Structure		ChemSpider 2019
CAS Registry Number	75-21-8	ATSDR 1990
Molecular Weight	44.05	ATSDR 1990
Physical State at 25°C	Gas	ATSDR 1990
Color/Form	Colorless gas	ATSDR 1990
Odor	Sweet, olefinic	ATSDR 1990
Synonyms	Ethylene oxide; oxirane; epoxyethane	ATSDR 1990
Solubility in water	$1x10^6$ mg/L	ATSDR 1990
Log K_{ow}	-0.22	ATSDR 1990
Vapor Pressure	$1.095x10^3$ mmHg	ATSDR 1990
Melting Point	-111°C	ATSDR 1990
Boiling Point	11°C	ATSDR 1990
Conversion Factors	1 ppm = 1.83 mg/m^3 1 mg/m^3 = 0.55 ppm	ATSDR 1990

Chapter 2 Major Sources and Uses

EtO is used as a chemical intermediate in the manufacture of ethylene glycol (antifreeze), polyester, detergents, polyurethane foam, solvents, medicine, adhesives, and other products. The conversion of EtO to ethylene glycols represents a major use for ethylene glycol in the US (IARC 2012). Relatively small amounts of EtO are used in sterilization of surgical equipment and plastic, as a fumigant, and as a sterilant for food (spices) and cosmetics (IARC 2012). In 2018, ethylene oxide was being produced in the US at 15 facilities in 11 locations by 9 companies. In the US, EtO is primarily produced in Texas and Louisiana ("Ethylene Oxide Frequently Asked Questions," 2018).

After the release of USEPA's 2014 National Air Toxics Assessment (NATA), the USEPA began to evaluate facilities that emit EtO. The 2014 NATA estimated that EtO significantly contributes to potential elevated cancer risks in some census tracts across the US; risk that is largely driven by the USEPA's recently-derived URF. Because of concerns related to cancer risk from EtO emissions raised by NATA, at least two EtO sterilizing facilities have closed or will close in 2019. In order to prevent shortages of critical medical equipment, the US Food & Drug Administration (USFDA) has been working with medical device manufacturers to find alternative locations and methods for sterilization. According to the USFDA, EtO is the likely sterilant for medical devices made from certain polymers (plastic or resin), metals, or glass, or that have multiple layers of packaging or hard-to-reach places (e.g., catheters). Approximately fifty percent of all sterile medical devices in the US are sterilized with EtO ("Ethylene Oxide Sterilization,"2019).

Sources of EtO emissions into the air include, but are not limited to, industrial emissions or venting with other gases. Other sources of EtO air emissions include its use as a sterilizer of medical equipment and its release from commodity-fumigated materials. The general population may be exposed to EtO through breathing ambient air containing EtO, smoking tobacco products, and breathing secondhand cigarette smoke ("Ethylene Oxide. 75-21-8"). Certain occupational groups (e.g., workers in EtO manufacturing or workers that use EtO to produce solvents, antifreeze, textiles, detergents, and polyurethane foam, sterilization technicians, and agricultural workers involved in fumigation) may be exposed in the workplace (IARC 2012).

EtO is also produced endogenously in the body due to oxidation of ethylene, which is generated by intestinal bacteria, lipid peroxidation of unsaturated fats, methionine, and hemoglobin. Recent analyses indicate that endogenous levels of EtO are significant relative to (i.e., higher than) doses corresponding to recently-derived regulatory values (USEPA 2016) and typical environmental exposures (Kirman and Hays 2017).

Chapter 3 Carcinogenic Potential

3.1 Carcinogenic Weight of Evidence (WOE)

EtO has been evaluated for carcinogenic potential by the International Agency for Research on Cancer (IARC), the US Environmental Protection Agency (USEPA), and the World Health Organization (WHO). These agencies' carcinogenic classifications for EtO are provided in Table 3 below.

Table 3: Carcinogenic Weight of Evidence

Group	Classification
IARC (2012)	Group I: Carcinogenic to humans
USEPA (2016)	Carcinogenic to humans
WHO (2003)	Highly likely to be carcinogenic to humans

Generally, the TCEQ only performs carcinogenic dose-response assessments for chemicals considered by the TCEQ either to be "Carcinogenic to Humans" or "Likely to Be Carcinogenic to Humans" (TCEQ 2015). For the purposes of this DSD, the TCEQ has adopted the USEPA (2016) carcinogenic classification for EtO, which is discussed further in Section 3.3.2.

3.2 Relevant Data

3.2.1 Epidemiological Studies

Based on the systematic review conducted by the TCEQ (Appendix A) as well as review of USEPA (2016) and other dose-response assessments (e.g., Valdez-Flores et al. 2010, Kirman et al. 2004), the assessment of excess cancer risk in the NIOSH and/or UCC cohorts provides the best basis for a carcinogenic assessment of EtO. These studies are summarized below.

3.2.1.1 NIOSH Cohort

Much of the following study summary is based on information from Section 4.1 of USEPA (2016).

The NIOSH retrospective cohort study of 17,530 workers in 13 sterilizing facilities (most recent follow-up by Steenland et al. 2004, 2003) provides adequate data for deriving quantitative cancer risk estimates (unit risk estimates or URFs) for EtO in humans. Briefly, the following are positive study attributes:

- Exposure estimates were derived for the individual workers using a comprehensive exposure assessment (although there are associated uncertainties);
- The cohort was large and diverse (e.g., 55% female); and
- There was little reported exposure to chemicals other than EtO.

EtO exposure estimates, including estimates for early exposures for which no measurements were available, were determined using a regression model that estimated exposures for each individual as a function of facility, exposure category, and time period. The regression model was based on extensive personal monitoring data from 18 facilities from 1976 to 1985 as well as information on factors influencing exposure, such as engineering controls (Hornung et al. 1994). Uncertainties are inevitably associated with historical exposure reconstruction. In this case, USEPA acknowledges that EtO measurement data were not available for most of the time that the cohort was exposed, errors in retrospective exposure assignments are inevitable, and that the exposure estimates are a primary source of uncertainty in the URF estimates (pp. 4-64 and 4-65 of USEPA 2016). Accordingly, to the TCEQ there appears to be appreciable uncertainty stemming from the lack of EtO exposure data prior to the time air monitoring data collection began when exposures for much of the cohort would have been relatively high and significantly contributed to cumulative exposure estimates (ppm-days, both unlagged and lagged), which appear likely to be biased low although a detailed discussion is beyond the scope of this DSD (e.g., Bogen et al. 2019, Li et al. 2019). The USEPA SAB agreed that these exposure estimates are likely of lower reliability (because there were no exposure measurement data that could be included in the exposure model prior to 1979) and actual EtO exposures were likely to have been higher than reflected in the estimates (p. I-41 of USEPA 2016). However, for the later monitoring data the regression model was able to account for 85% of the variation in average EtO exposure levels when evaluated against independent test data from the same set of data. The investigators estimated the cumulative exposure (ppm × days) for each individual worker by multiplying the estimated exposure (ppm) for each job (exposure category) held by the worker by the number of days spent in that job and summing over all the jobs held by the worker.

The TCEQ notes that this worker population was exposed to extraordinarily high concentrations of EtO. For example, Tables IV and V of Hornung et al. (1994) provide measured and estimated worker exposure means of 3.5-4.6 ppm, which are ≈1,000,000-2,000,000 times higher than central tendency environmental levels (i.e., background and environmental exposure means ≈0.0024-0.0034 ppb per USEPA 2016). Animal carcinogenicity studies were conducted at even higher EtO exposure concentrations (10-100 ppm; see Section 3.2 of USEPA 2016). On any given day, estimated exposure for a job could have ranged from 50-77,000 ppb (pp. D-4 and D-37 of USEPA 2016), which is remarkably ≈15,000-32,000,000 times higher than central tendency environmental levels of EtO. Consequently, when USEPA (2016) discusses model fit in the "low-dose" region, the low-dose region for these workers provides no information about the shape

of the dose-response at environmental levels. High-dose carcinogenicity data alone are incapable of informing truly low-dose risk, no matter how extensive the analyses or peer review (i.e., other relevant information must be duly considered).

In regard to study findings, Steenland et al. (2004) present follow-up results for the cohort mortality study previously discussed by Steenland et al. (1991) and Stayner et al. (1993). Positive findings in the current follow-up include statistically increased (lympho)hematopoietic cancer mortality in males of the highest EtO exposure group (see Tables 4, 6, and 7 of the study) and statistically increased breast cancer mortality in females of the highest EtO exposure group (see Tables 5 and 8 of the study). Steenland et al. (2003) present results of a breast cancer incidence study of a subcohort of 7,576 women from the NIOSH cohort that showed statistically increased odds ratios for the highest exposure group (see Tables 4 and 5 of the study).

3.2.1.2 UCC Cohort

Swaen et al. (2009) redefined and updated the UCC cohort of male workers employed in industrial facilities where EtO was produced or used. Previous studies of the UCC cohort were published by Greenberg et al. (1990) and Teta et al. (1993). All 2,063 men were employed between 1940 and the end of 1988 and were observed for mortality through 2003. Workers from EtO departments at the Kanawha Valley, WV sites hired after 1988 were determined to have no appreciable EtO exposure and were, therefore, not added to the cohort. Cause-specific standardized mortality ratios (SMRs) were calculated. Internal analyses were made by applying Cox proportional hazards models to the data.

The exposure assessment for this update relies on the qualitative categorization of EtO producing and using departments by exposure level developed by Greenberg et al. (1990), and on quantitative estimates of average intensity by these department categories and by time period (1925-1988) developed by Teta et al. (1993). Time period cut points were chosen as follows: 1925, the start-up of EtO production in the Kanawha Valley; 1940, start of cohort observation and first period with published estimates of exposure; 1957, chlorohydrin process for EtO production completely shut-down; and 1974, the period when airborne exposures declined substantially due to process and exposure controls. The combination of the average exposure for the four different time periods and the three classifications of departments into low, medium, and high exposure departments created the exposure matrix. Cumulative EtO exposure (ppm-years) for each study subject was then estimated by multiplying the estimated time-period and department-specific exposure concentrations by duration in months for each individual's assignments to EtO departments and summing the products over all assignments up through December 1988 (Swaen et al. 2009). The average cumulative EtO exposure was 67.16 ppm-years (≈16,118 ppm-days, as 67.16 ppm-years × 240 days/year), about twice that of the NIOSH cohort. As of Swaen et al. (2009), the average follow-up period for the UCC cohort

was 10 years longer (36.5 versus 25.8 years) and the percent deceased was 3-fold greater than the NIOSH cohort (51% versus 16%). However, the number of expected cancer deaths for the UCC cohort (a measure of study power) was between 2-3 times less because of the significantly smaller cohort size in both number and person-years (e.g., 75,306 versus 450,906 person-years). Nevertheless, this is an important cohort that contributes to the human EtO carcinogenicity database. For example, the long follow-up period and relatively high cumulative exposure estimates are advantageous for the identification of potential long-term carcinogenic effects.

As mentioned above, uncertainties are inevitably associated with historical exposure reconstruction. In addition to finding fault with the cohort for being smaller and limited to males, USEPA (2016) characterizes the EtO exposure assessment for the UCC cohort as more uncertain than that for the NIOSH cohort (e.g., greater likelihood for exposure misclassification, use of surrogate exposure data; see Section 4.1 of USEPA 2016). However, the NIOSH cohort appears to have unemphasized yet significant uncertainties of its own; most notably, the lack of exposure data prior to the mid-70's when exposures were likely to have been significant and would have increased cumulative exposure estimates for much of the cohort (e.g., Bogen et al. 2019). Ultimately, the TCEQ finds that these cohorts provide the best basis for a regulatory dose-response assessment for EtO, and cohort-specific results will be appropriately weighed based on relevant statistical criteria.

Regarding study findings, Swaen et al. (2009) report that no indications were found for excess cancer risks from EtO exposures, including the lymphohematopoietic malignancies (e.g., 11 leukemia deaths occurred and 11.8 were expected, 12 non-Hodgkin's lymphoma deaths occurred and 11.5 were expected). Cox proportional hazards modeling for all cause, leukemia, and lymphoid malignancies mortality revealed no trends or associations with cumulative EtO exposure. In recognition of exposure estimate uncertainty, it is also important to note that no statistically significantly elevated SMRs were found in the analysis by hire date, and there were no statistically significant increases in the longest duration category and no suggested trends by duration (all surrogates of exposure). Study authors concluded that the cohort showed no long-term carcinogenic effects associated with EtO exposure.

Similarly, an as of yet unpublished update of the UCC cohort through 2013 (submitted as Bender et al.) concludes that examination of mortality from all causes of death, all cancers, leukemia, non-Hodgkin's lymphoma, and lymphoid malignancies revealed no evidence for an exposure-related response; EtO exposure in this cohort was not associated with an observable increase in lymphohematopoietic cancer mortality (personal communication with study co-author Ciriaco Valdez-Flores). The average cumulative dose of EtO (67 ppm-years) is reported to be around two times that for the NIOSH cohort, with a ≈63% longer follow-up period (≈41 years) and a similar number of lymphoid cancer deaths in males (27 in NIOSH versus 25 in UCC) despite the

number of person-years for males in the NIOSH cohort (189,868 person-years) being significantly greater than that in the UCC cohort (83,524 person-years).

3.2.2 Animal Studies

Human (i.e., epidemiological) data are available for a carcinogenic assessment of EtO and are preferred over animal data for toxicity factor (i.e., URF) development (TCEQ 2015). Therefore, animal carcinogenicity data are not discussed herein. See Section 4.2 of USEPA (2016) for relevant information.

3.3 Mode of Action (MOA) and Carcinogenic Classification

The TCEQ has adopted the overall USEPA (2016) EtO MOA analysis and carcinogenic classification determinations for the purposes of this DSD (note that this does not necessarily mean that the TCEQ necessarily fully concurs with every USEPA statement or characterization). As such, summary information was essentially derived directly from Sections 3.4.3 and 3.5.1 of USEPA (2016) and is presented below, with references to USEPA (2016) document sections removed [*emphasis added*]. The references for the studies supporting the information below can be found in the aforementioned sections of USEPA (2016).

3.3.1 MOA

In this section, the evidence for a mutagenic MOA for EtO carcinogenicity is analyzed under the MOA framework in the USEPA's 2005 Guidelines for Carcinogen Risk Assessment (USEPA 2005a).

The hypothesis is that EtO carcinogenicity has a mutagenic MOA. This hypothesized MOA is presumed to apply to all the tumor types. The key events in the hypothesized mutagenic MOA are: (1) DNA adduct formation by EtO, which is a direct-acting alkylating agent; (2) the resulting heritable genetic damage, including DNA mutations, particularly in oncogenes and tumor suppressor genes, as well as chromosomal alterations; and (3) the clonal expansion of mutated cells during later stages of cancer development; eventually resulting in (4) tumor formation. Mutagenicity is a well-established cause of carcinogenicity.

Is the hypothesized MOA sufficiently supported in the test animals?

Consistent with the USEPA's 2005 Guidelines for Carcinogen Risk Assessment (USEPA 2005a), this MOA analysis for a mutagenic MOA is organized around the Hill "criteria" (or considerations) developed for the analysis of epidemiological studies (Hill 1965). These considerations are denoted in *underlined italics* in the discussion below.

Numerous studies have demonstrated that EtO forms protein and DNA adducts, in mice and rats, and there is incontrovertible evidence that EtO is mutagenic and genotoxic. The evidence

for causal associations between the key events and tumor formation has *strength* and *consistency*. Increases in the frequency of gene mutations in reporter genes have been observed in the lung, T-lymphocytes, bone marrow, and testes of transgenic mice and in T-lymphocytes of rats exposed to EtO via inhalation at concentrations similar to those inducing tumors in the rodent carcinogenesis bioassays. In addition, in the lung, uterine, mammary gland and Harderian gland tumors from EtO-exposed mice in those bioassays, dramatic shifts toward guanine and adenine mutations have been observed in the mutational spectra of the proto-oncogenes *Hras* and *Kras*, as well as the tumor suppressor *Trp53*, consistent with the propensity of EtO to form DNA adducts on purine bases.

Inhalation studies in laboratory animals have also demonstrated that EtO exposure levels in the range of those used in the rodent bioassays induce sister chromatid exchanges (SCEs) in several species and consistently induce chromosomal aberrations in mice. In rats, although SCEs are consistently observed in the available studies, the results for micronuclei formation and chromosomal aberrations following subchronic (up to 4-week) inhalation exposures to EtO at the same exposure levels as those used in the rodent bioassays have been nonpositive; however, IARC (2008) has noted analytical limitations with some of these analyses. In addition, Donner et al. (2010) demonstrated a clear duration effect in mice, with chromosomal aberrations being induced at those same EtO exposure levels only following longer exposure durations (≥12 weeks).

Specificity is not expected for a multisite mutagen and carcinogen such as EtO (USEPA 2005a). A *temporal relationship* is clearly evident, with DNA adducts, point mutations, and chromosomal effects observed in acute and subchronic assays.

Dose-response relationships have been observed between EtO exposure *in vivo* and DNA adducts, SCEs, and *Hprt* and *Trp53* mutations. A mutagenic MOA for EtO carcinogenicity also clearly comports with notions of *biological plausibility* and *coherence* because *EtO is a direct-acting alkylating agent. Such agents are generally capable of forming DNA adducts, which in turn have the potential to cause genetic damage, including mutations; and mutagenicity*, in its turn, is a well-established cause of carcinogenicity. This chain of key events is consistent with current understanding of the biology of cancer.

In addition to the clear evidence supporting a mutagenic MOA in test animals, there are no other compelling hypothesized MOAs for EtO carcinogenicity. For example, there is no evidence of cytotoxicity or other cellular dysfunction indicative of regenerative proliferation, and little-to-no evidence supporting some other toxicity-related MOA, such as oxidative stress.

Is the hypothesized MOA relevant to humans?

The evidence discussed above demonstrates that EtO is a systemic mutagen in test animals; thus, there is the presumption that it would also be a mutagen in humans. Moreover, human evidence directly supports a mutagenic MOA for EtO carcinogenicity. Several studies of humans have reported exposure-response relationships between hemoglobin adduct levels and EtO exposure levels (e.g., van Sittert et al. 1993, Schulte et al. 1992), demonstrating the ability of EtO to bind covalently in systemic human cells, as it does in rodent cells. DNA adducts in EtO-exposed humans have not been well studied, and the evidence of increased DNA adducts is limited. EtO has yielded positive results in *in vitro* mutagenicity studies of human cells. Although the studies of point mutations in EtO-exposed humans are few and insensitive and the evidence for mutations is limited, there is clear evidence from a number of human studies that EtO causes chromosomal aberrations, SCEs, and micronucleus formation in peripheral blood lymphocytes, with some evidence of positive relationships with exposure concentration and duration.

USEPA (2016) indicates that there is strong evidence that EtO causes cancer in humans, including some of the cancer types observed in rodent studies (i.e., lymphohematopoietic cancers have been observed in both rats and mice and mammary carcinomas have been observed in female mice), providing further weight to the relevance of genotoxicity to the development of cancer in humans. USEPA (2016) concludes that *the weight of evidence supports a mutagenic MOA for EtO carcinogenicity*. Although oxidative stress or other processes might contribute to the development of EtO-induced cancers, the TCEQ agrees that the available evidence best supports a mutagenic MOA as the primary process mediating EtO-induced carcinogenicity (USEPA 2016).

3.3.2 Carcinogenic Classification

Regarding carcinogenic classification under USEPA (2005a), while USEPA (2016) states that there is substantial evidence that EtO exposure is causally associated with lymphohematopoietic cancers and female breast cancer in human studies, the agency acknowledges that *the evidence is not strong enough to be conclusive*. Of the seven relevant Hill "criteria" (or considerations) for causality (Hill 1965), *temporality*, *coherence*, *biological plausibility*, and *analogy* are readily satisfied, and the other three criteria (*consistency*, *biological gradient*, and *strength of association*) are satisfied to varying degrees. For example, there is "*some* evidence of dose-response relationships", but "there is *little strength* in the associations, as reflected by the modest magnitude of most of the RR [relative risk] estimates." See Section 3.5.1 of USEPA (2016) for additional discussion on these criteria. USEPA (2016) ultimately concludes that *the overall epidemiological evidence for causal associations between EtO exposure and lymphohematopoietic cancer as well as female breast cancer is strong but less than conclusive, with epidemiology study evidence for other cancer types (e.g., stomach cancer and pancreatic cancer) also being inadequate*.